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A novel polycondensate containing cyclodextrin and lactose: Synthesis, metal-complexing properties, and degradation

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Abstract

The synthesis and characterization of the novel water-soluble polycondensate from β-cyclodextrin triazine and D-lactose are described, which represents the first copolymer containing cyclodextrin and lactose in the main-chain. In addition, the metal complex forming properties of the novel polymer for different metal ions such as Cr(III), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Sr(II), Cd(II), Pb(II), and Al(III) were studied using the liquid-phase polymer-based retention (LPR) method and compared with those of β-cyclodextrin. According to the retention profiles obtained by the LPR method, all 10 metal ions investigated showed a strong interaction with this polymer. Finally, this polycondensate was shown to be microbiologically degradable with exponential microbial growth of 45 CFU (10^8 mL^{-1}) by using conventional microbiological methods.

Keywords: Cyclodextrin; Lactose; Polycondensate

1. Introduction

Cyclodextrins (CDs), containing the unique property of forming inclusion complexes due to the relatively different hydrophilicity at the interior and exterior of their cavity, have been the subject of many research groups and found applications in pharmacy, food, cosmetics, toiletries, and agrochemicals [1–3]. As one of the examples using their capability to form non-covalent inclusion complexes with numerous lipophilic molecules, CDs also can associate into the structure of nanoparticles for the entrapment of drugs such as progesterone [4]. Synthetic polymers with natural building blocks such as carbohydrates have been studied increasingly due to their potential as biocompatible materials with medical applications such as cell–cell interactions [5] and cellular recognition [6,7].

Our goal for this study was the synthesis of a novel water-soluble polymer containing cyclodextrin in the main-chain with the potential for environmental and biomedical applications due to the natural building block of lactose.

2. Experimental

2.1. Materials and instruments

The triazine derivative of β-cyclodextrin was a gift from Wacker-Chemie (Germany) and D-lactose was purchased from Sigma and used without further purification. β-Cyclodextrin was purchased from Fluka (>99%) and purified by ultrafiltration before the metal complexation. All metal salts were used in the form of nitrates and purchased from Junsei, except Ni(II) (Aldrich), Cr(III) (Janssen, Germany), Pb(II), Sr(II) (Yakuri, Japan), and Al(III) (chloride, Merck). K_2HPO_4 (Aldrich, 98+%), KH_2PO_4 (Oriental Chemical Industry (OCI), extra pure), $(NH_4)_2SO_4$ (OCI, extra pure), $MgSO_4 \cdot 7H_2O$ (OCI, extra pure), dextrose (OCI, anhydrous), Bacto-agar (Difco), $ZnSO_4 \cdot 7H_2O$ (Aldrich, reagent), $FeSO_4 \cdot 7H_2O$ (Aldrich, reagent), EDTA disodium salt (Aldrich), $MnSO_4 \cdot H_2O$ (Sigma, ACS reagent), $CuSO_4$

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(Aldrich, 98%), $Co(NO_3)_2 \cdot 6H_2O$ (Aldrich, reagent), and $Na_2B_4O_7 \cdot 10H_2O$ (Aldrich, reagent) were used as received.

The *Pseudomonas* basal mineral medium consisted of K_2HPO_4 (12.5 g), KH_2PO_4 (3.8 g), $(NH_4)_2SO_4$ (1.0 g), $MgSO_4 \cdot 7H_2O$ (0.1 g), anhydrous dextrose as a carbon source (0.8 M, 100 mL), and 5.0 mL of trace element solution ($ZnSO_4 \cdot 7\,H_2O$ (1.1 g), $FeSO_4 \cdot 7H_2O$ (0.5 g), EDTA disodium salt (0.29 g), $MnSO_4 \cdot H_2O$ (0.154 g), $CuSO_4$ (0.026 g), $Co(NO_3)_2 \cdot 6H_2O$ (0.025 g), and $Na_2B_4O_7 \cdot 10H_2O$ (0.018 g) in 100 mL distilled water).

FT-IR spectra (KBr pellets) were recorded on a Perkin–Elmer 2000 series, UV–vis spectra on a Perkin–Elmer Lambda 12, ^1H NMR spectra on a FT-NMR spectrometer (Varian UNITY plus 300, 300 MHz) and molecular mass was measured by light scattering (Malvern 4700C). Specific viscosities for the optimum reaction time were determined at 25 °C using a Micro-Ubbelohde viscometer with suspending ball-level (Schott). Thermal gravimetric analysis was performed with a TGA 2050 (TA Instruments) and the concentrations of metal ions were determined by inductively coupled plasma spectrometry (ICP, Thermo-Jarrell Ash IRIS/AP). For the microbiological degradation experiments, the turbidity was measured by a turbidimeter (HS Scientific, Portable Turbidirt DRT-15CE), an autoclave (Auto Clave DAC 811) and a clean bench (DVB 912 of Daeil Engineering) were used. The morphological features were measured by using a scanning electron microscope (JEOL, JSM-5800).

2.2. Metal complexation studies

For the determination of the complex binding ability, a solution of the 10 metal nitrates was placed into the filtration cell containing the polymer or β-cyclodextrin solution. The volume in the cell was kept constant at 20 mL with a concentration of the polymer of 1 wt% and a metal ion of each concentration 20 mg L^{-1}. The pH of the cell and the reservoir solutions was adjusted to 5, and the system was pressurized with N_2. A membrane with a nominal molar mass cut-off (MMCO) of 1 kg mol^{-1} (Amicon) was used. The filtrate fractions ($Z = 1–10$) were collected and subjected to analysis by inductively coupled plasma spectrometry.

2.3. Synthesis of poly(β-cyclodextrin triazine-co-D-lactose) (PCL)

An aqueous solution (3 wt%) of D-lactose (**2**: 150 mg, 0.44 mmol) was added dropwise to a 5% solution (pH 11.3) of β-cyclodextrin triazine (**1**: 0.593 g, 0.44 mmol) under stirring for 2 h in an ice-water bath. The mixed solution was then stirred at room temperature for 12 h after addition of D-lactose. Then the viscous solution was neutralized with 0.1 M hydrochloric acid, diluted, freeze dried after purification by ultrafiltration (Amicon membrane, nominal molar mass exclusion limit of 1 kg mol^{-1}). Yield: 0.70 g, retention: 94%.

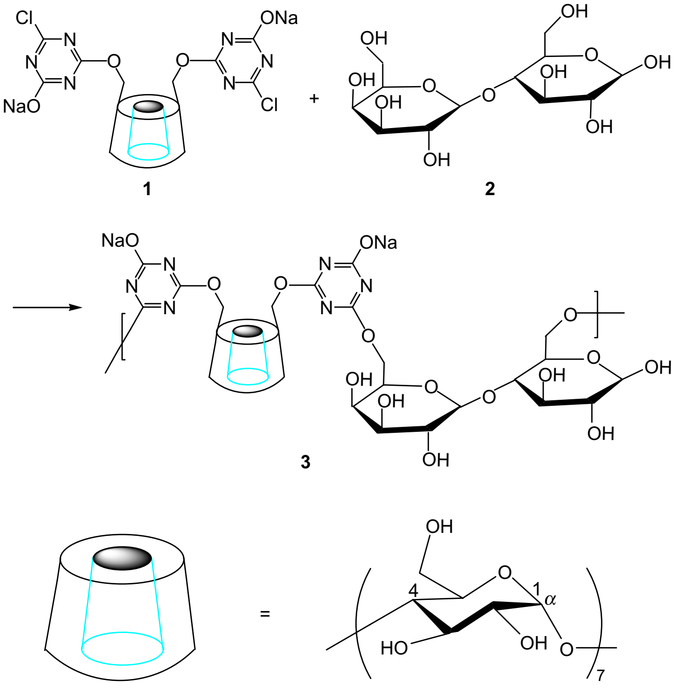
3. Results and discussion

3.1. Synthesis

Poly(β-cyclodextrin triazine-*co*-D-lactose) (PCL, **3**) was synthesized by polycondensation of the β-cyclodextrin triazine derivative (**1**) and D-lactose (**2**) (Scheme 1). The product was a white solid, soluble in water, DMSO, and partially in DMF and $CHCl_3$. The molecular mass was found to be 21.6 kg mol^{-1} by light scattering measurement after purification by ultrafiltration (MMCO: 1 kg mol^{-1}).

The FT-IR spectral data (Fig. 1) clearly showed an evidence of polycondensation between β-cyclodextrin triazine and D-lactose with the appearance of a new band ascribed to the C=O stretching vibration (1718 cm^{-1}) of aldehyde arising out of the reducing sugar component of lactose, while the homopolymer of β-cyclodextrin triazine showed no C=O stretching vibration. The ^1H NMR spectral resonance signals (Fig. 2) of PCL and β-cyclodextrin triazine look similar due to same structure except a shoulder signal at $\delta = 3.30$ ppm of PCL. It might stem from lactose, which has a different chemical environment after the polyreaction with β-cyclodextrin triazine, when compared to β-cyclodextrin triazine. Thus, the copolymer **3** (21.6 kg mol^{-1}) is the first water-soluble polymer containing both building blocks cyclodextrin and lactose in the main-chain. Very few reports in this area dealt with cyclodextrin-pendant polymers [8], however, cyclodextrin-containing polymers showed a molecular mass as low as 3–4 kg mol^{-1} [9,10], and others with lactose-pendant polymers [11–13].

In order to assess the thermal stability of the polymer and its copper complex a thermogravimetric study has been



Scheme 1. Polycondensation of β-cyclodextrin triazine (**1**) and D-lactose (**2**) yielding the cyclodextrin-lactose copolymer **3**.

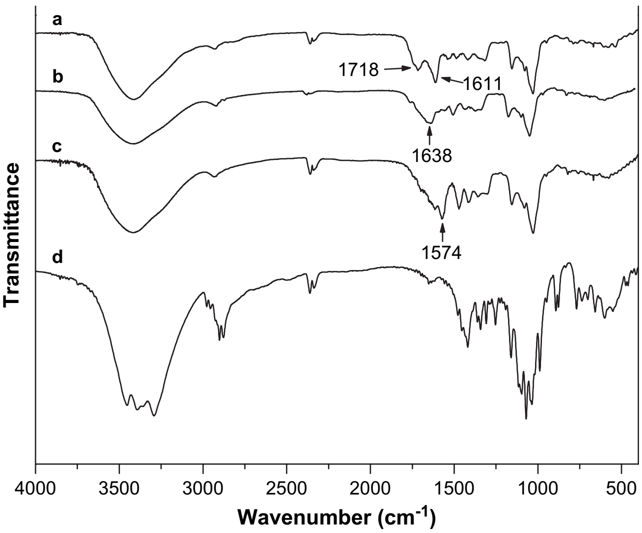


Fig. 1. FT-IR spectra of (a) poly(β-cyclodextrin triazine-*co*-D-lactose), (b) homopolymer of β-cyclodextrin triazine, (c) β-cyclodextrin triazine, and (d) D-lactose.

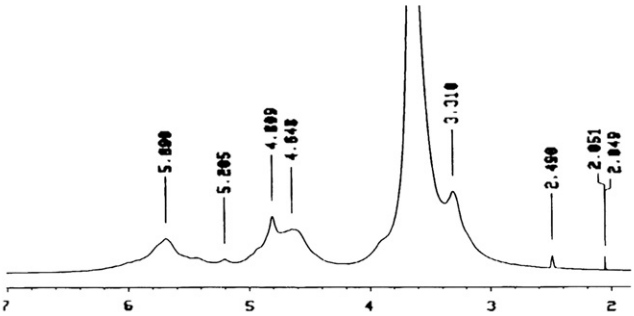


Fig. 2. ^{1}H FT-NMR spectrum of poly(β-cyclodextrin triazine-*co*-D-lactose) (PCL, **3**; in DMSO-d_6).

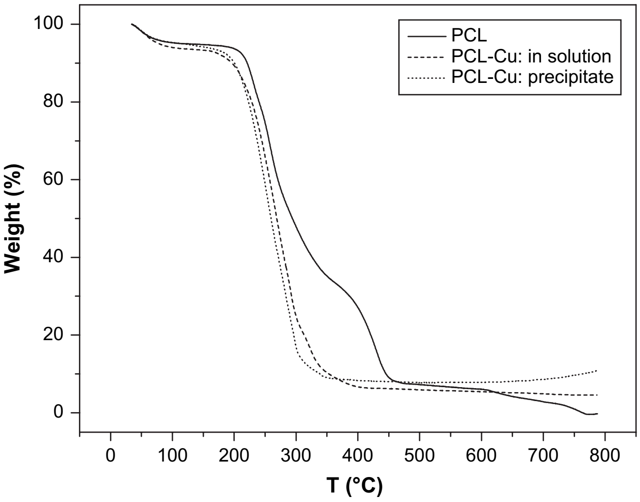


Fig. 3. Thermogravimetric analysis of poly(β-cyclodextrin triazine-*co*-D-lactose) (PCL, **3**) and its Cu(II) complexes (PCL–Cu).

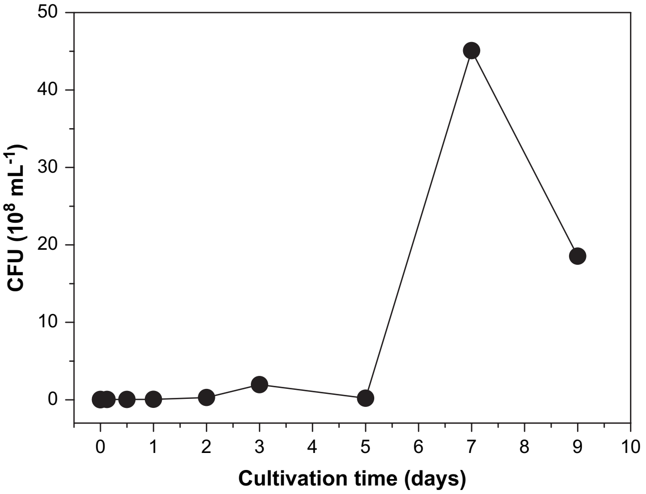


Fig. 4. Microbiological degradation of poly(β-cyclodextrin triazine-*co*-D-lactose) based on the colony-forming unit (CFU) as a function of cultivation time.

conducted (Fig. 3). The degradation pattern shows that in the case of the pristine polymer, an initial steady weight loss was observed up to 190 °C and the weight loss reached 10% at 220 °C. At temperatures >220 °C, the weight loss showed two $T_{\max}$, 260 °C and 423 °C.

For the assessment of the polymer biodegradation, a batch test procedure was used with a solid medium. To monitor the degradation process based on the microbial growth, the colony-forming units (CFU) were counted and assessed as an indicator for the degradability (Fig. 4). Also, the degradability of polymer **3** was compared with the turbidity of buffer and medium solution (Fig. 5).

The complexing properties of the water-soluble polymer **3** for 10 divalent and trivalent ions were investigated by using the liquid-phase polymer-based retention (LPR) technique

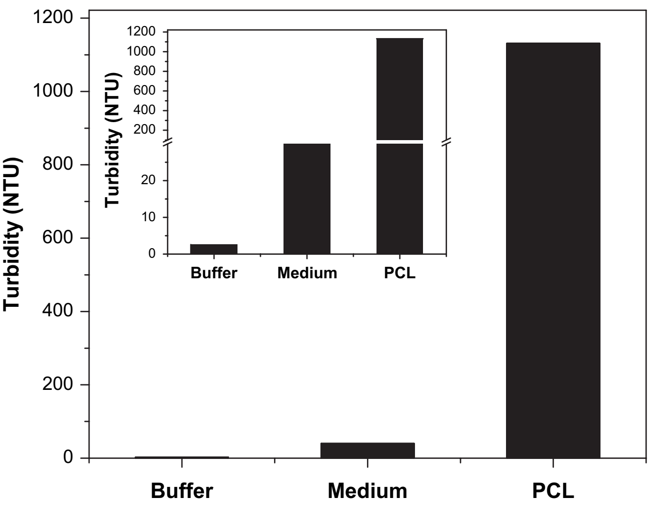


Fig. 5. Turbidity of the microbe-inoculated solution of poly(β-cyclodextrin triazine-*co*-D-lactose) (PCL, **3**). Buffer was 0.1 M potassium phosphate buffer (pH 7.2) at 25 °C consisting of 71.7 mL of 1 M K_2HPO_4 and 28.3 mL of 1 M KH_2PO_4; medium was mineral medium solution. (NTU = nephelometric turbidity unit).

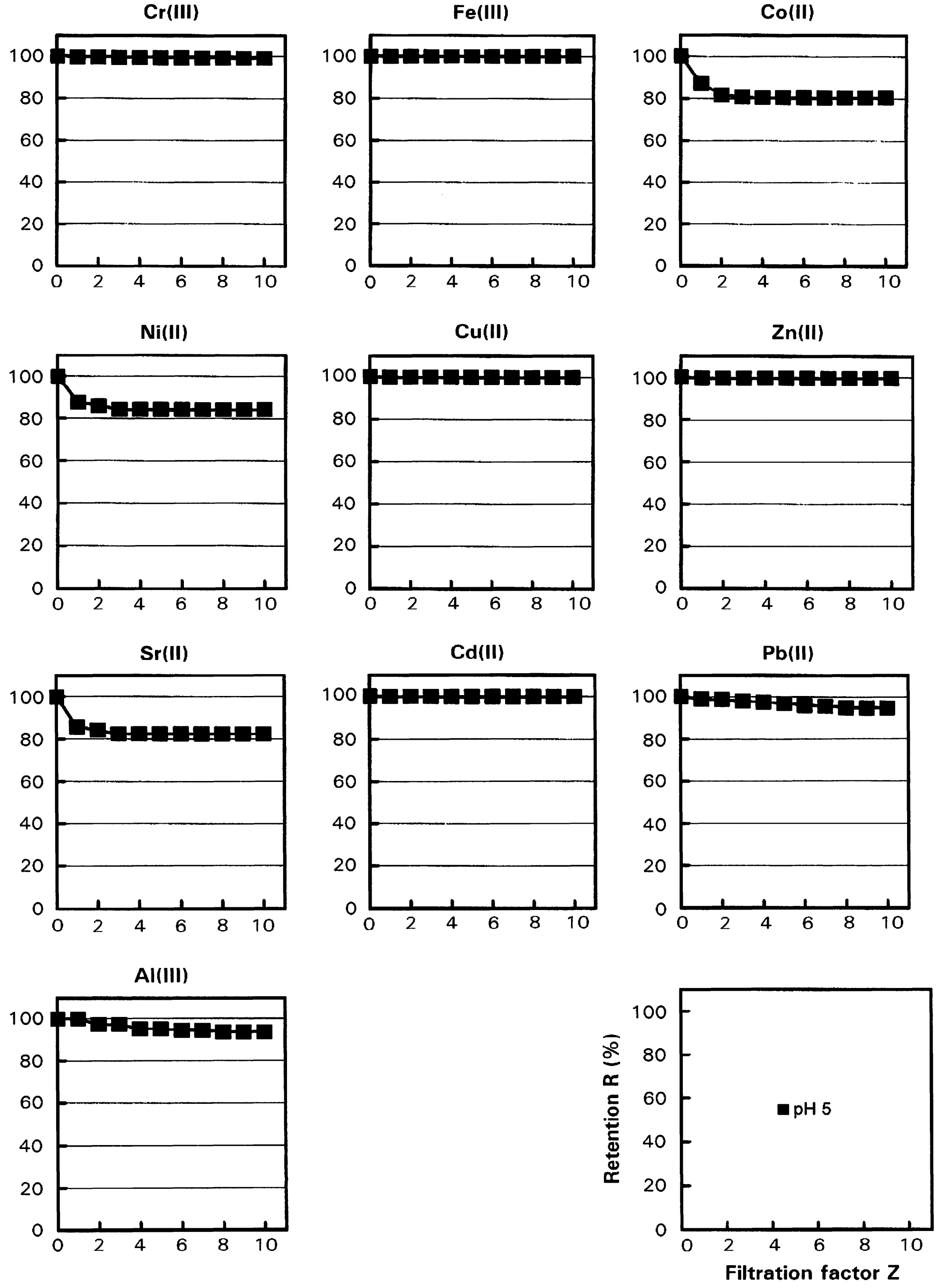


Fig. 6. Retention profiles of poly(β-cyclodextrin triazine-*co*-D-lactose) (PCL) (1 wt%) for 10 metal ions at pH 5 using the liquid-phase polymer-based retention (LPR) method. $R(\%) = c_r/c_o \times 100$: where c_r is the metal concentration in the retentate (the cell solution after a filtrate volume of V_f has been passed) and c_o is the initial metal concentration in the cell. $Z = V_f/V_o$: where V_f is the volume of filtrate and V_o is the volume of cell solution. A polychelatogen concentration of 1 wt% in the cell solution was sufficient for quantitative complexation, as the polymer contained a great excess of complexing groups in comparison with the low metal concentration (20 mg L^{-1}).

[14–17] and β-cyclodextrin was compared to polymer **3** as a control. This method yielded retention profiles, which are plots of the retention *R* versus the filtration factor *Z*, yielding an indicator for the metal-complexing ability in the aqueous phase. The retention of metal ions in solution by a polymeric reagent can be calculated as follows:

$$R(\%) = c_r \times c_o^{-1} \times 100$$

where c_r is the metal concentration in the retentate after a filtrate volume of V_f has been passed and c_o is the initial metal concentration.

Z is defined as the ratio of the volume of filtrate V_f and the volume of cell solution V_o:

$$Z = V_f \times V_o^{-1}$$

Typical retention profiles of polymer **3** are shown in Fig. 6. A strong metal complexation ($R = 100\%$) took place only with Cr(III) and Fe(III) ions from the 10 metal ions studied (Co(II), Ni(II), Cu(II), Zn(II), Sr(II), Cd(II), Pb(II), and Al(III)) with retention values of 60% and 100%, respectively. These results are similar to that of β-cyclodextrin which was found to be a very specific binding agent for Fe(III) due to the fact that Fe(III) can easily form complexes with sugars [18]. However, the novel polymer PCL shows a strong metal complexation ($R = 100\%$) for all metal ions, except for Co(II), Ni(II), and Sr(II) that showed a slightly lower retention than 100% with values of 80%. This strong metal complexation of polymer **3** can be ascribed to the synergetic effects such as the triazine moiety of the β-cyclodextrin precursor, the lactose group of PCL, and a polymer cooperative effect.

In this report the novel water-soluble copolymer containing cyclodextrin and lactose in the main-chain is described. In the metal complexation studies, this copolymer showed a very strong metal complexation with most metal ions investigated when using the LPR method. Both the unique property of forming inclusion complexates by the cyclodextrin moieties and the sugar lactose can enhance the application potential of this copolymer for drug delivery and metal ion removal.

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